RELEASE RATES OF LEVONORGESTREL FROM SILASTIC[R] CAPSULES, HOMOGENEOUS RODS AND COVERED RODS IN HUMANS

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ABSTRACT

Three forms of subdermal implants containing levonorgestrel are described. These are: capsules, in which the powdered drug is sealed inside of lengths of Medical Grade Silastic tubing; homogeneous rods, in which the drug is uniformly dispersed in Silastic 382 Medical Grade Elastomer; and covered rods, in which a core rod of drug and filler-free polydimethylsiloxane polymer (50:50, Wt:Wt) are sealed inside thin-walled Silastic tubing.

Long-term *in vivo* release rates from human subjects are presented; 6.5 years for capsules, 3.6 years for homogeneous rods and 4 years for covered rods. Sets of six capsules release a decreasing amount of drug through the first few hundred days *in situ* and after 500 days a fairly constant rate of about 35 micrograms per day is released (2 µg/cm). Homogeneous rods deliver a continuously declining amount of drug during the entire time studied. In the first 100 days the release averages 136 micrograms per day from a set of three 3-cm rods (15 µg/cm), gradually declining to 30 micrograms per day (3.3 µg/cm) from day 800 to day 1300. The covered rods deliver at a constant rate of 17.5 micrograms per day for a 3-cm rod (5.83 µg/cm) through 4 years.

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CONTRACEPTION

INTRODUCTION

The use of polydimethylsiloxane (Silastic^{R}) to fabricate devices containing contraceptive steroids for subdermal implantation began with the pioneering work of Segal and Croxatto (1). Their proposal that such a system could serve as the basis for long-term, reversible, steroidal contraception in women was quickly pursued by Croxatto with implants made from Silastic Medical Grade tubing containing the synthetic progestin, chlormadinone acetate in 1968, with a first report in 1969 (2). Following this early lead, the International Committee for Contraception Research (ICCR) of the Population Council, Inc., undertook a broad-based program to investigate candidate progestins and suitable carriers for subdermal implants in order to develop an effective, long-term, low-dose progestin-only contraceptive method. The goal was to develop a safe, effective and reversible method of contraception that would last up to 5 years with but a single intervention. Pilot clinical studies, particularly those of Croxatto (3) and Coutinho (4) indicated that the progestins, levonorgestrel, norgestrienone and megestrol acetate were promising candidates for use in subdermal implants. In July 1975, the ICCR undertook a randomized, double-blind study of these three progestins to determine the most suitable drug(s) for further development of this modality of contraception. Early in the study megestrol acetate was withdrawn from the market in the United Kingdom because of the development of breast nodules in beagle dogs and the ICCR investigators elected to withdraw this drug from the study and a comparable group of women were recruited to use the TCu 200 IUD.

The first year results indicated a very low pregnancy rate of 0.6 per 100 woman-years for the levonorgestrel capsule implants, good acceptability of the implant method with both steroids and continuation rates of 75 to 80 percent (5). Analysis of steroid remaining in the capsules after various periods of time revealed that only about 10% of the initial load of levonorgestrel was delivered in one year to the women (6), indicating the potential for an effective life of several years. These studies have been extended and expanded in order to gather long-term effectiveness data. An early open study of levonorgestrel capsules by Croxatto's group is now well into the sixth year and the results of the first 5 years of experience are in press (7). In this study, analysis of steroid remaining in the capsules after removal has permitted calculation of *in vivo* release rates of levonorgestrel through 6 years.

Two other forms of Silastic implants containing levonorgestrel have also been tested by ICCR clinics over the past several years. These are the homogeneous rod form, molded from Silastic^{R} 382 Medical Grade Elastomer containing 25% by weight of levonorgestrel, and a "covered rod" form, made from the same polymer used in the 382 formulation, but without the filler material, and encased in thin-walled Silastic Medical Grade tubing. Some of the results of clinical testing of these forms have been published (8-11) and several other ICCR-sponsored studies

are still in progress.

Previous reports on levonorgestrel release from capsules and rods have encompassed relatively short times, one to two years.

We now report in vivo release rate data through six years for subdermal Silastic capsules containing levonorgestrel (tradenamed NORPLANT™*), through three years for homogeneous rods and through four years for covered rods.

MATERIALS AND METHODS

Levonorgestrel for all implants was donated by Wyeth International, Philadelphia, Pa.

Silastic®** materials were purchased from or donated by The Dow Corning Corporation, Midland, Michigan.

The capsule implants were manufactured for The Population Council by Laboratorios Gutfol, S.A., Mexico City, Mexico.

The homogeneous rods and the covered rods were manufactured for The Population Council by Leiras Pharmaceuticals, Huhtamaki Oy, Turku, Finland.

Description of Implants

Capsule implants contain dry crystalline levonorgestrel sealed inside of Medical Grade Silastic tubing with Medical Adhesive A. They are 2.41 mm outside diameter and 1.57 mm inside diameter. They are 34 mm in total length with the central 30 mm containing levonorgestrel.

Homogeneous rods contain 25% by weight of levonorgestrel homogeneously dispersed in Silastic 382 Medical Grade elastomer. They are 2.44 mm in diameter and 3 cm in length.

Covered rods contain a core of levonorgestrel in polydimethylsiloxane without filler (50:50 Wt:Wt) sealed inside Medical Grade Silastic tubing. They are 34 mm in total length with a drug core length of 30 mm.

* NORPLANT™ is The Population Council's trademark for subdermal implants containing levonorgestrel.

** Silastic® is the Registered Trademark for The Dow Corning Corporation's brand of polydimethylsiloxane.

Placement and Removal Procedures

All implants were placed subdermally through a 5-mm incision in either the ventral aspect of the forearm or the inner aspect of the upper arm after infiltration with a local anesthetic (3,5). A #10 trocar was used. Removal was effected through a small (5 mm) incision, preferably in the same spot used during placement.

The data reported here is from subjects who used six capsules, 3 homogeneous rods or either 4 or 6 covered rods. Removals were made whenever the subject decided she no longer wished to use the method and all implants were removed at a single visit.

In Vivo Release Rates

As implants were removed from subjects in the ICCR cooperating clinics, they were returned to the New York laboratories of The Center for Biomedical Research of The Population Council for determination of levonorgestrel remaining in the devices.

Capsule implants were manufactured to a standard of ± 1 mg levonorgestrel content. Recovered implants were assumed to have originally contained the amount equal to the average assay content for the lot when manufactured. Steroid loss was calculated by subtracting the amount found on assay of the recovered implants from the original average content of the capsules in a lot.

Rod forms of the implants, both homogeneous rods and covered rods, were also manufactured to a standard of ± 1 mg. In addition, each set of rods was weighed to the nearest milligram so that, on recovery, release rates could be checked both from assay of remaining steroid and by weight loss of each set. Early work in rats had shown that loss in weight of the devices was entirely attributable to steroid loss.

Levonorgestrel assays were performed by exhaustive extraction of the steroid with methylene chloride, dilution to a suitable volume with ethanol and quantitated by absorbance spectrophotometry at the U.V. maximum absorbance peak of 240 nanometers, in comparison with a standard sample of levonorgestrel.

Recovered sets of rods were cleaned, dried and weighed to the nearest milligram to obtain weight loss prior to extraction of the steroid.

RESULTS

Capsules

Figure 1 is a plot of milligrams lost from 142 sets of capsules vs. days *in situ*. There is a relatively rapid drop in release rate during the first few hundred days of use, as previously reported (6). From 500

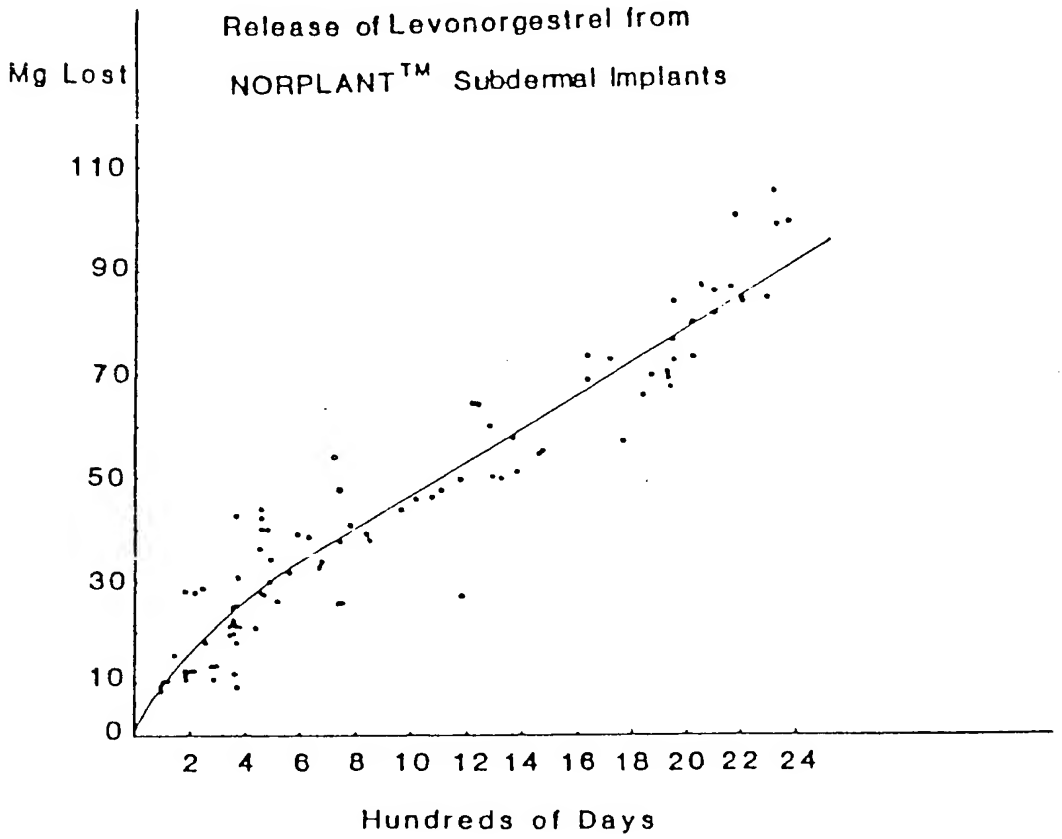

Fig. 1: Release of levonorgestrel from sets of six 3-cm Silastic capsules: milligrams vs. days *in situ*. Each point represents total steroid lost from a set of six capsules in a subject for the indicated length of time.

days through 2375 days (6.5 years), the 63 entries in this time span reveal a release rate averaging 34.6 μg per day. Linear regression analysis of these data gives a slope of 0.0346 mg per day with a correlation coefficient of 0.8655 ($p<<.001$). There is, of course, considerable scatter in the data and some subjects receive somewhat less and others somewhat more than the average dose. This is similar to the 30 μg per day release rate recently reported by Diaz *et al.* for the same time interval (7). Even after 6.5 years, the capsules still contain 50% of the original content.

Homogeneous Rods

Figure 2 is a plot of milligrams lost from 117 sets of three 3-cm rods containing 25% by weight of levonorgestrel. There is a continuous drop in release rate throughout the entire time span of the data, through 1316 days (3.6 years), but there is considerably less scatter in the data with the rods than in the case of the capsules.

In the figure, the release rates for the four time intervals presented are calculated from linear regression analysis of the data in each time span. By this method these mean rates for each time interval are statistically significant values of the average release of drug ($p<.01$). These data sets are all from loss of weight while *in situ*.

To check the validity of the use of weight loss as a measure of steroid loss, we also extracted the steroid from 37 sets and measured the amount remaining by U.V. spectrophotometry. The mean difference between the two sets of values was only 0.76 milligrams and the correlation coefficient was 0.9904.

Covered Rods

Figure 3 is a plot of milligrams lost from a single 3-cm covered rod implant vs. time. These data were derived from clinical studies in which four 3-cm covered rods and six 3-cm covered rods had been used, reduced for presentation to a single 3-cm covered rod for each subject.

For the 53 entries, covering the period from 92 days through 1469 days, a linear regression analysis generates a line with a slope of 0.0175 mg per day (17.5 μg/day) with a correlation coefficient of 0.9828 ($p<<.001$). Subjects using four of these devices would thus have received an average dose of 70 μg per day of levonorgestrel and those using six of them would have received an average dose of 105 μg per day.

To check the validity of the use of weight loss as a measure of steroid loss, we also extracted the steroid from 27 of the sets and measured the amount remaining by U.V. spectrophotometry. The mean difference between

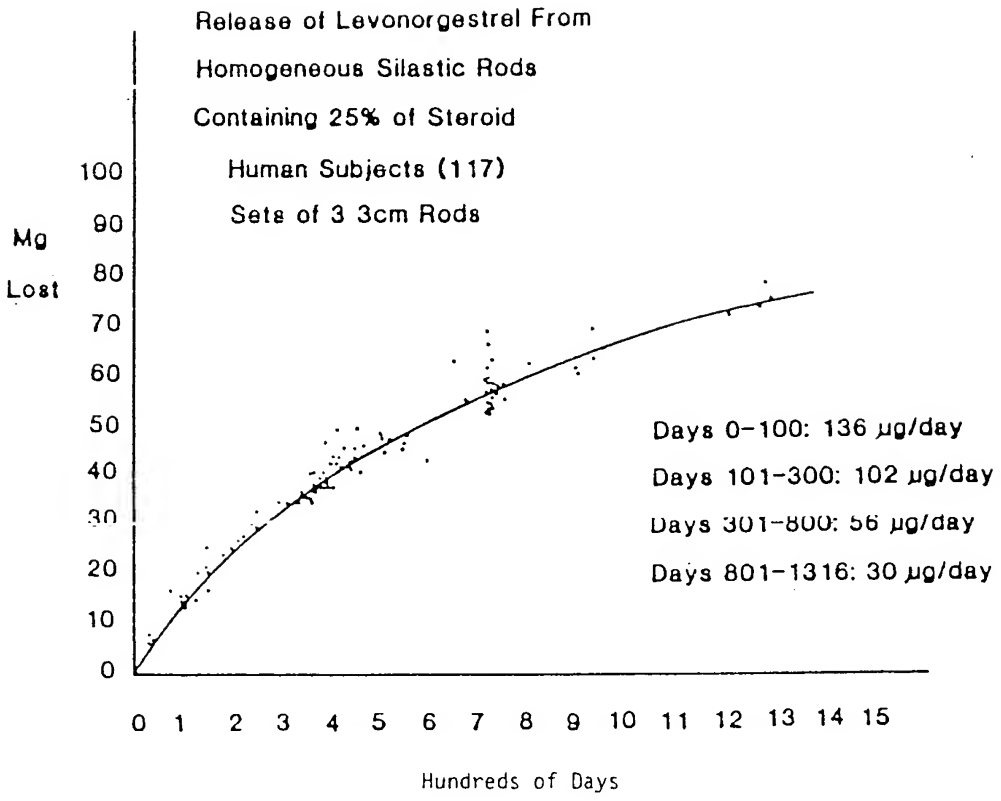

Fig. 2: Release of levonorgestrel from homogeneous Silastic rods. Milligrams per set of 3 vs. time.

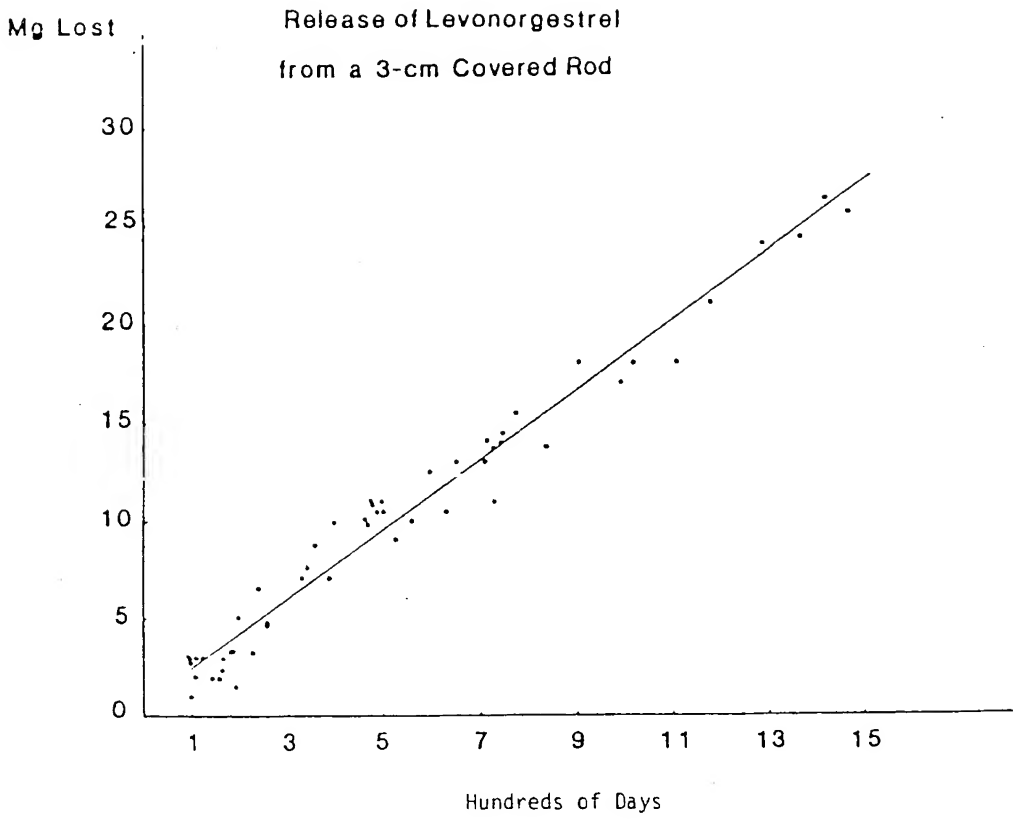

Fig. 3: Release of levonorgestrel from a single 3-cm covered rod, in milligrams vs. time. Slope = 0.0175, r = 0.9828.

the two sets of values was less than one milligram and the correlation coefficient was 0.976.

DISCUSSION

This report considerably extends the *in vivo* experience previously reported for capsules and homogeneous rods containing levonorgestrel (6) and provides data on release from covered rods not previously reported.

Factors known to affect the rate of release of drugs from silicone rubber devices have been adequately discussed (6) and will only be briefly reviewed here. Major factors are the rate of dissolution into the polymer, solubility of the drug in the polymer, rate of diffusion through the polymer and rate of dissolution from the surface of the device into the surrounding milieu, in this case the human body.

Each of the three types of implants reported on here will be discussed separately.

Capsules

As previously reported (6), the rate of release of levonorgestrel from capsules decreases with time *in vivo* for the first few hundred days and there are large individual variations from subject-to-subject but not from capsule-to-capsule within a set for a given individual. After about 500 days, the average rate of release levels off and becomes relatively constant through 2375 days (6.5 years), but individual variation is clearly apparent (Figure 1).

It has long been known that formation of a fibrous capsule around a silicone rubber implant is a general phenomenon in animals (12) and is particularly evident in women with silicone mammary prostheses (13), which are, of course, very much larger than the implant capsules. These fibrous capsules uniformly consist primarily of collagen, do not adhere to the silicone rubber and have a smooth "glassy" appearance on the surface next to the rubber. There is also wide variation in the thickness of these fibrous capsules, both between species and from individual-to-individual within a species and the process of encapsulation may proceed for months or even years until equilibrium is achieved (12,13). In guinea pigs this "pseudosheath" around silicone implants is well defined within 8 days and continues to change in composition and thickness for a year, but once the silicone implant is removed, the resolution of the sheath begins and is complete within two weeks (14).

The present report on release rates in women seem to support the concept of the formation of a collagen-containing fibrous sheath around the implants that may continue for several hundred days before equilibrium is achieved. Certainly, such a sheath does form to varying degrees which is apparent when the implants are removed. Others have suggested (15) formation of such a capsule but no other reported studies have extended beyond one year.

We have also observed that capsules become filled with fluid after several months or years *in situ*. This fluid is water with only tiny traces of other molecular species appearing on a mass spectrometer scan of the water.

Thus, the mechanism of release rate control may be at least two-fold, the formation of a fibrous sheath around the implant and the ingress of water to provide a saturated solution of steroid bathing the inner surface of the capsule. The fibrous sheath would gradually slow the rate of release until equilibrium is achieved and the gradual ingress of water would ultimately result in a constant concentration of steroid presented to the inner surface of the capsule.

This mechanism of release rate control is certainly not the only possible one but does appear to be a major factor in these long-term studies.

Homogeneous Rods

The rate of release from these rods is much higher initially than with the capsules and continuously declines over the 1316 days (3.6 years) for which data is available (Figure 2). In this case individual variation is far less marked, resulting in a fairly smooth release rate curve.

In this case the drug is homogeneously dispersed throughout the rod, and, as the drug reservoir is depleted, a drug-free zone is generated, progressing inward from the outer surface of the rod. This zone of depletion is easily seen when a recovered rod is sliced through its diameter. The result of this depletion is a continuously increasing drug-free Silastic layer through which the steroid must diffuse to reach the surface of the device, and the diameter of the drug-containing core is decreasing.

If the increasing distance that the drug must travel through the depletion zone is the controlling factor in the rate of release from the device (matrix control) rather than the other possible controlling factors of rate of dissolution of drug in the matrix, rate of diffusion through the matrix or rate of diffusion into the boundary layer around the implant, then the cumulative amount of drug released should be directly proportional to the square root of time, $t^{1}/_{2}$ (16).

In the present set of data, cumulative drug loss vs. $t^{1}/_{2}$ calculation gives a correlation coefficient of 0.9808 ($p<<.001$), with the conclusion that release from these devices is, indeed, matrix-controlled.

The data were generated by measuring the loss in weight of the implants, under the assumption that the loss in weight was attributable entirely to loss of steroid. To check this assumption, we extracted the steroid

from 37 sets of implants, after weighing them, and measured the amount of steroid remaining in the implants. Subtracting these values from the average steroid content as measured on control sets of manufactured sets of implants gave the amount of steroid loss by an independent method.

Comparison of the values derived by the two methods results in a correlation coefficient of 0.9904 ($p<<.001$). It is therefore valid to use weight loss only in calculating release rates. Also, this gives assurance that no non-steroidal material is released from the devices and that nothing is absorbed from the body that is not removed by simple drying.

Covered Rods

As seen in Figure 3, the rate of release of levonorgestrel from these covered rods is essentially zero order. Linear regression analysis of the 53 entries gives a slope of 0.0175 (17.5 μg/day) for a 3-cm device with a correlation coefficient of 0.983.

The data in the fourth year of use is limited but linear regression analysis of the 6 points in the 4th year gives a slope of 0.0227 (22.7 μg/day) with a correlation coefficient of 0.93, giving some confidence that release rates have not declined in the fourth year. At the end of four years, 50% of the original load of drug remains, giving a theoretical lifetime of 8 years. In practice this seems unrealistic but 5 or 6 years appears possible.

The exact mechanism by which a constant rate of release is achieved over a four-year span with relatively little individual variation can only be speculative but certain criteria must be satisfied for this result. The steroid must be presented to the surface of the device at a rate that presents a constant concentration to the surrounding tissue. This result can be achieved only by maintaining a constant concentration at the surface of the covering membrane and this can only result from a comparatively high dissolution rate of the steroid into the core polymer and a high rate of diffusion within the core polymer. The rate-limiting step must be either the rate at which the steroid diffuses through the covering membrane or the rate at which the surrounding tissue can carry it away. Since the homogeneous rods have been shown to deliver much more steroid to the tissue than do the covered rods, the rate-limiting step is most probably the rate of diffusion through the membrane.

In conclusion, we believe that the covered rod configuration can be very useful in delivering levonorgestrel at a controlled, constant rate.

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